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# Accepted Manuscript

## Prevalence and Comorbidities of Double Diabetes

S.R. Merger, W. Kerner, M. Stadler, A. Zeyfang, P. Jehle, M. Müller-Korbsch, R.W. Holl

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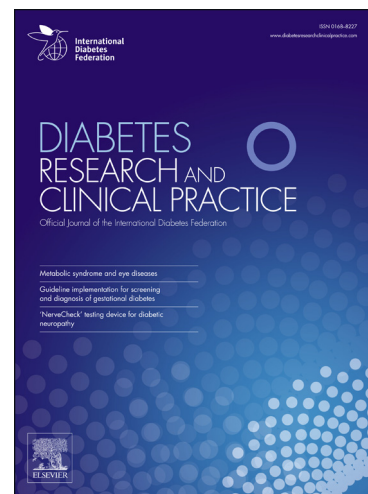
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# Prevalence and Comorbidities of Double Diabetes

**Running title:** *Double Diabetes*

S. R. Merger<sup>1</sup>, W. Kerner<sup>2</sup>, M. Stadler<sup>3</sup>, A. Zeyfang<sup>4</sup>, P. Jehle<sup>5</sup>, M. Müller-Korbsch<sup>6</sup>, R. W. Holl<sup>7</sup>, for the DPV Initiative and the German BMBF Competence Network Diabetes mellitus

Institutions: <sup>1</sup>Division of Endocrinology, Department of Internal Medicine, Ulm University; <sup>2</sup>Klinikum Karlsburg, Department of Diabetes; <sup>3</sup> King's College London, Diabetes Research Group, Denmark Hill Campus, 10, Cutcombe Road, SE5 9RS London, UK; <sup>4</sup>Hietzing Hospital Vienna, 3rd Medical Department, Wolkersbergenstr. 1, 1130 Vienna, Austria; <sup>5</sup>Bethesda Hospital Stuttgart, Hohenheimer Strasse 21, 70184 Stuttgart, Germany; <sup>6</sup>Evangelisches Krankenhaus, Wittenberg, Department of Internal medicine; <sup>7</sup>Wilhelminenspital Wien, Department of Internal Medicine; <sup>7</sup>University of Ulm, Institute of Epidemiology and Medical Biometry, ZIBMT, Ulm, Germany, German Center for Diabetes Research (DZD)

Address correspondence to:

Sigrun R. Merger

Division of Endocrinology, Department of Internal Medicine, Klinikum Coburg, Würzburg University

Ketschendorferstr.33, 96450 Coburg, Germany

Tel: +49-9561-22-6329

Fax: +49-9561-22-6399

Email: [sigrun.merger@online.de](mailto:sigrun.merger@online.de)

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**Conflicts of interest** The authors have no conflict of interest to declare.

**Key words:** double diabetes, T1DM, diabetes mellitus type 1, insulin resistance, diabetic nephropathy, macroangiopathy, microangiopathy, coronary heart disease, LADA

**Novelty statement:** The outlined paper analyzes 392 diabetes centers with 31119 patients with autoimmune diabetes for the prevalence and comorbidities of double diabetes. We could show for the first time that insulin requirement or insulin resistance is an independent risk factor for patients with type 1 diabetes and that even in well controlled diabetes an additional metabolic syndrome is a major risk factor for developing macrovascular as well as microvascular complications.

**Abbreviations:** BMI: body mass index; DCCT: Diabetes Control and Complications Trial; DD: double diabetes; DPV: Diabetes-Verlaufs-Dokumentation; EDC: Epidemiology of Diabetes Complications study; GAD-AB: glutamatdecarboxylase antibodies; HDL: high density lipoprotein; LDL: low density lipoprotein; MS: metabolic syndrome; NCEP: National Cholesterol Education Program; PAD: peripheral arterial disease; T1DM: diabetes mellitus type 1; T2DM: diabetes mellitus type 2; UKPDS: United Kingdom Prospective Diabetes Study

## Abstract

**Background:** A growing number of people with type 1 diabetes (T1DM) are identified with features of metabolic syndrome (MS) known as “double diabetes”, but epidemiologic data on the prevalence of MS in T1DM and its comorbidities are still lacking.

Aim of this cross sectional study is to better estimate the prevalence of MS in T1DM, and to assess its association with comorbidities.

**Methods:** Data of 31119 persons with autoimmune diabetes mellitus were analyzed for signs of MS and presence of late complications. Double diabetes was defined as T1DM coexisting with MS (obesity, hypertension, dyslipidemia). Multiple linear or logistic regression analyses were performed to identify associations between double diabetes and late complications.

**Results:** 25.5% (n=7926) of persons with T1DM presented additionally the MS. Persons with double diabetes showed significantly more macrovascular comorbidities (coronary heart disease 8.0 versus 3.0% w/o MS, stroke 3.6 versus 1.6%, diabetic foot syndrome 5.5% versus 2.1%). Also microvascular diseases were increased in people with double diabetes (retinopathy 32.4% versus 21.7%, nephropathy 28.3% versus 17.8%). Both macrovascular and microvascular comorbidities were increased independent of glucose control, even if patients with good metabolic control (HbA1c <7.0%, 53mmol/mol) showed significantly less macrovascular (coronary heart disease 2.3% versus 1.8%,  $p<0.0001$ ) and microvascular problems (retinopathy 8.7% versus 6.6%,  $p<0.0001$ ).

**Conclusions:** Double diabetes seems to be an independent and important risk factor for persons with T1DM in developing macrovascular and microvascular comorbidities. Therefore, patients should be identified and development of MS should be avoided. Longterm studies are needed to observe the effect of insulin resistance on patients with autoimmune diabetes.

## 1. Introduction:

Autoimmune diabetes mellitus (Type-1DM) with an autoimmune loss of insulin producing beta cells has for quite a long time been clearly separated from MS and diabetes mellitus type 2, where insulin resistance and a relative insulin deficiency is the more relevant pathophysiology [1]. During the last years increasing evidence demonstrated, that the clinical phenotype of people with T1DM presents with a broad range of clinical features and that increasing numbers of patients show signs of MS as abdominal obesity, arterial hypertension, dyslipidaemia, , up to now not considered a clinical feature of diabetes mellitus type 1 [2, 3]. These persons often have a family history of type 2 diabetes (T2DM) [4] or hypertension [5]. Genetic similarities are seen between obese people with autoimmune diabetes and T2DM [6]. The prevalence of persons showing signs of both diabetes forms increases significantly because of lifestyle changes in the last decades with increasing obesity and decreasing physical activity, but epidemiologic data about this phenomenon are still scarce [2, 7, 8]. Recently, the combined presentation of features of both type 1 and type 2 diabetes has been referred to as “double diabetes”, e.g. when a person with T1DM becomes overweight/obese and insulin resistance increases [3, 7, 9].

Aim of the following study is to analyse the prevalence of MS - defined according to the NCEP (National Cholesterol Education Program) criteria as obesity, dyslipidaemia and arterial hypertension combined with insulin resistance - in people with T1DM [10].

## **2. Materials and Methods:**

### **2.1. Patients and data documentation**

Patients were selected from the DPV [Diabetes-Verlaufs-Dokumentation] registry, a computer-based documentation program for all diabetes-related aspects of diagnosis and patient care. The database includes patients with all types of diabetes and is currently used by 392 specialized centres of the DPV Initiative from Germany and Austria. Prospectively documented data, after anonymisation, are transmitted twice a year from participating health care facilities to the central database in Ulm, Germany, for quality assurance and statistical analysis [11, 12]. Implausible

and inconsistent data are reported back to the centres of origin for verification and correction. The DPV Initiative, and analyses based on anonymised data in the DPV database, are approved by the Ethics Committee of the University of Ulm, Germany.

For the present analysis, data from patients aged  $\geq 18$  years with a clinical diagnosis of insulin dependent T1DM were selected. Diabetes mellitus type 1 was defined as initially insulin dependent diabetes mellitus with at least one diabetes specific antibody. Data transmitted prior to September 2013 were included into this analysis. Up to this time-point, 40046 patients  $\geq 18$  years were registered in DPV, 32871 showed all necessary data including BMI and insulin dose, patients who had a co-medication of sulfonylurea or who had no documented diabetes-specific antibodies were excluded ( $n=1752$ , leaving  $n=31119$  participants in the analysis). Information about gender, age, and diabetes duration was available for all subjects. For analysis of glycaemic control, individual mean HbA1c was standardized to the Diabetes Control and Complications Trial (DCCT) normal range by the “multiple of the mean method” [13] based on the local HbA1c reference ranges, HbA1c was measured by immunological tests, LDL by ultracentrifugation.

Diabetes associated kidney diseases were classified according to the German National Diabetes Guideline [14] into microalbuminuria (albumin excretion in morning urine 20-200 mg/l) and macroalbuminuria ( $>200$  mg/l). Dyslipidemia and arterial hypertension are defined according to the NCEP criteria [10].

MS was defined according to the NCEP criteria, if participants show at least three criteria out of obesity (waist circumference  $> 40$  inches in male,  $>35$  inches in female or  $BMI > 30 \text{ kg/m}^2$ ), hyperglycaemia present in all participants since all are diagnosed with diabetes mellitus, dyslipidaemia or arterial hypertension [10]. Of all 31119 documented people with T1DM, 7926 fulfilled the criteria of the MS (double diabetes, DD), the rest ( $n=23193$ ) were considered type 1 diabetic persons without MS (T1DM w/o MS). To discriminate effects of blood glucose control from those of MS a subgroup analysis for people with well controlled diabetes as defined by

HbA1c <7% (53mmol/mol) was performed (n= 9203, double diabetes n= 1892, no double diabetes n=7311) (Fig.1).

## 2.2. Statistical analysis

For categorical variables, proportions were used for description. As not all continuous parameters were normally distributed based on QQ plots, descriptive statistics with mean values and standard error were calculated for continuous variables. For unadjusted group comparisons, Kruskal-Wallis-test for continuous variables and  $X^2$ -test for binary variables were used. Bonferroni-stepdown adjustment was used to correct p-values for multiple testing.

To consider possible confounding effects as sex, age or diabetes duration on the comparison between type-1-patients and double-diabetes-patients, linear regression models were created with treatment centre as random effect. Iterations were optimized according to Newton-Raphson, and denominator degrees of freedom were calculated by the between-within-method (SAS, proc glimmix). For binary variables, multivariable logistic regression models were created. Adjusted means/percentages (LS-Means) were calculated for 40-year-old patients with a diabetes duration of 15 years, assuming equal numbers of men and women. Regression models were implemented for all patients, as well as separately for patients with good metabolic control defined by HbA1c  $\leq 7\%$ , 53mmol/mol.

All statistical analyses were implemented with SAS 9.4 (Statistical Analysis Software, SAS Institute, Cary, NC, USA). A two-sided p-value <0.05 was considered statistically significant.

## 3. Results

### 3.1. Study population

In the DPV database, 31119 adult people (>18 years) with diabetes mellitus type 1 were identified (table 1). 7926 (25.4%) met the definition of MS (double diabetes) [10]. Baseline

characteristics of patients with and without metabolic syndrome are presented in Table 1 and Table 2.

People with double diabetes had developed diabetes at a higher age (24.9 years, IQR 25.6 versus 15.8 years, IQR 19.7) and showed a higher percentage of males (Table 1). Mean age in the double diabetes group (DD) was 44.7 years  $\pm$  18.6 versus 36.2 years  $\pm$  18.3. Diabetes duration was longer in people with T1DM with MS (Table 1). Metabolic control as measured by HbA1c was worse in persons with double diabetes (mean HbA1c 8.5(69mmol/mol)  $\pm$  0.051% versus 8.0 $\pm$ 0.048%,  $p < 0.0001$ ), when adjusted for age, sex and diabetes duration.

Persons with double diabetes required a significantly higher daily insulin dose (Table 2), as well as a higher dose per kg body weight. This effect was even more significant when adjusted for age, sex, and diabetes duration. In well controlled diabetes (HbA1c  $< 7\%$  (53mmol/mol),  $p < 0.0001$ ) daily insulin requirement did show a similar difference but persons had a lower insulin need per kg bodyweight when adjusted for age, sex and diabetes duration (Table 2) compared to the entire group. Dyslipidaemia was also seen in people with T1DM without MS (84.1% in DD versus 53.9%, Table 2). After adjustment for demographic differences cholesterol levels were higher in double diabetes, HDL was lower, LDL was higher, even if a higher percentage of people with double diabetes were taking lipid lowering medication (27.8% versus 10.3%). Arterial hypertension was still more frequent in coexisting MS, even if more people with double diabetes were on antihypertensive medication (47.2 versus 18.4%) (Table 1). Smoking habits were not significantly different in both groups (28.5% versus 27.3%,  $p = 0.2283$ ) but smoking was significantly more present in DD patients once adjusted for age, sex and diabetes duration (Table 2). People with well controlled diabetes had a lower proportion of smokers, both in the DD and the only T1DM groups (Table 2).

Persons with double diabetes did not show significant differences in beta cell antibody distribution compared to people with T1DM without MS: GAD-AB (glutamatdecarboxylase antibodies) 87.8 versus 86.1%,  $p=0.986$ , IA2 antibodies 68.4 versus 69.2%,  $p=0.842$ , (Table 2).



Additional autoimmune diseases were seen in both groups as well: about one quarter had thyroid antibodies (Table 2). Antibodies to tissue transglutaminase are seen in 16.9% of the people with double diabetes and 15.3% of persons without MS ( $p=0.18$ ), but clinical diagnosis of coeliac disease differs only in people with  $HbA1c < 7\%$  (53mmol/mol) (Table 2).

### 3.2. Macrovascular diseases

People with T1DM and MS showed a significantly higher prevalence of macrovascular diseases (Fig. 2), especially of ischemic heart disease (8% versus 3%,  $p < 0.0001$ ). This effect is seen in all patients (Fig. 2). In well controlled diabetes the difference between persons with and without MS is less pronounced (2.7% versus 1.3%). However adjusted for age, gender and diabetes duration this effect remains highly significant (2.6% versus 1.4%,  $p < 0.0001$ ). The lowest risk is seen in well controlled T1DM without MS (Fig.2). The macrovascular problems take place even if the patients with MS had significantly more antihypertensive (47.2% versus 18.8%) and lipid lowering drugs (24.5% versus 9.1%). Myocardial insufficiency is defined according to the National Guidelines as reduced pump function [15].

A history of stroke was twice as common in people with double diabetes compared to T1DM without MS (Fig. 2). Adjusted for age, gender and diabetes duration, the difference is highly significant (1.39% versus 0.87%,  $p < 0.0001$ ). The same effect is seen in adjusted data for diabetic foot syndrome [16, 17] (1.3 versus 0.76,  $p < 0.0001$ ) and PAD (0.4% versus 0.24%,  $p < 0.0001$ ). In people with good blood glucose control, PAD and diabetic foot syndrome were reduced to less than half (Fig.2,  $p < 0.0001$ ), but again two times as frequent in persons with double diabetes ( $p < 0.0001$ , Fig. 2).

### 3.3. Microvascular diseases

The same pattern is seen in microvascular complications: persons with double diabetes show an increased risk for retinopathy and nephropathy (Fig. 3). Adjusted for age, gender and diabetes duration, 16.2% of subjects with double diabetes showed diabetic retinopathy versus 12.4% of T1DM without MS ( $p<0.0001$ ). For proliferative retinopathy the frequencies were 8.0% versus 5.4% ( $p<0.0001$ ). Subgroup analysis in people with HbA1c $<7\%$  (53mmol/mol) showed a lower prevalence of diabetic retinopathy in both groups (8.7% with versus 6.6% without MS,  $p<0.0001$ ), but compared to the macrovascular comorbidities, risk reduction was less dependent on MS than on good metabolic control. Nephropathy is also seen more often in T1DM with MS (Fig. 3). Adjusted for demographic factors, 22.6% of the people with double diabetes showed microalbuminuria (3.6% a macroalbuminuria) compared to 16.03% (1.96%) of the T1DM without MS (both  $p<0.0001$ ). The well controlled subgroup with MS displayed 6.8% microalbuminuria compared to 5.0%, in people without MS ( $p<0.0001$ ). For macroalbuminuria the frequencies were 1.4% versus 0.9% ( $p<0.0001$ ). Taking together, double diabetes is an independent risk factor for all microvascular comorbidities even if good metabolic control seems to show a bigger impact (Fig.3).

#### 4. Discussion

The phenotype of T1DM mellitus changed in the last decades [3]. Life style changes with a lack of physical activity and high caloric food as well as better medical care with intensified insulin therapies in persons with insulin dependent diabetes result in an increasing number of obese subjects with T1DM. In this cross sectional analysis of a cohort of 31119 people with T1DM mellitus, 30.9% ( $n=9616$ ) were overweight, 13.5% obese (Table 2). Compared to DCCT (BMI  $23.5\pm 2.9$  kg/m<sup>2</sup> [18]), or the diabetomobile study (BMI  $24.2$  kg/m<sup>2</sup> [19]), BMI of our study cohort was  $25.27\pm 6.09$  kg/m<sup>2</sup> (Table 2), so average BMI increased remarkably in people with type1 diabetes over the last 20 years. One possible reason is the change in therapy of T1DM over the last decades: Whereas early patients with T1DM were trained to a strict diet and a non-

flexible insulin regimen to avoid diabetes complications, multiple daily insulin injection regimen according to the basis bolus principle allow for more flexible mealtimes and more frequent snacks, which could contribute to weight gain [13]. Eating behaviour also changed during the last decades with more fast food eaten also by people with diabetes mellitus type 1. Especially dietary fat seems to have a major impact on insulin resistance and body weight [20]. But obesity is not the only risk factor in people with T1DM: 57.6% (n=17471) of all T1DM analysed showed either elevated blood pressure or took antihypertensive drugs, 61.6% (n=19167) showed dyslipidaemia (Table 2). So using the NCEP criteria [10], 25.5% (n=7926) of the study cohort showed the MS together with T1DM (Table 2). In people with well controlled T1DM mellitus, 20.6% (n=1892) showed double diabetes. In people with MS the quality of blood sugar control was significantly worse than in T1DM without MS (Table 1, 2). But only 51.3% of our analysed people with autoimmune diabetes had a normal body mass index (Table 1) which is only slightly better than the average non diabetic German population where only 48% have a normal body mass index [21]. Therefore increasing interest should be directed to the field of double diabetes, defined as T1DM mellitus with criteria of the MS [2, 7, 8, 22]. Since patients with MS show an augmented cardiovascular risk, increasing effort should be taken to identify persons with T1DM and MS to reduce their mortality.

Kilpatrick et al. showed in a cohort of 1337 patients that estimated glucose disposal rate as a marker of insulin resistance is linked to a higher risk of cardiovascular diseases [2]. So these patients showed a higher insulin need than non double-diabetes patients. Our data verify this effect in 31119 persons (table 2). In our study, double diabetic persons needed significantly more daily insulin in total as well as per kg bodyweight. This is especially interesting, because previous studies could not see a significant difference in the daily amount of insulin, probably due to the small number of persons analysed [2]. So the daily need of insulin seems to be an easy marker to estimate insulin resistance in insulin dependent diabetes persons. Subjects with good blood glucose control had a tendency to need less insulin. One possible explanation might be that

people with better metabolic control show more interest in their health and do more sports, which lowers the insulin need and the body weight. Clinical experience also underlines that insulin requirement depends on blood sugar control even if clinical trials addressing this topic are rare [23]. Also these patients more often show different eating behaviours and possibly consume fewer calories. Another possibility could be reduced stress in patients with good blood glucose control and therefore lower stress hormone levels which decreases insulin resistance [24, 25]. Insulin regimen thereby did not show any relevant differences, besides that the obese persons use slightly more often insulin pumps (CSII) and slightly less often conventional insulin therapy whereas no significant difference in intensified conventional therapy was seen (Table 1). The autoimmune characteristics did not show significant differences between double diabetes and T1DM without MS (Table 1, 2) but people with double diabetes develop diabetes at a higher age, so probably genetic differences also contribute to the risk of double diabetes [26]. So since the genetic burden of the metabolic syndrome is quite high, it might also be possible, that people with DD inherit the T2DM genes from their parents on top of the T1DM, here genetic analysis should be carried out in people with DD.

People with double diabetes show a significant increase in all macrovascular comorbidities, especially in myocardial infarction (Fig. 2) [27]. Although it is well established that good metabolic control reduces the risk of macro- and microvascular endpoints and mortality [28, 29], MS is an independent risk factor for the development of comorbidities: The participants with double diabetes and HbA1c below 7% (53mmol/mol) had a significantly higher prevalence of macrovascular complications than well controlled persons with T1DM without MS 7% (Fig. 2). This highlights that MS is an independent cardiovascular risk factor in patients with T1DM. Insulin resistance is known to have a major impact on the cardiovascular outcome of patients with T2DM [30], but it seems to be a major risk factor in patients with T1DM as well (Fig. 2) [2]. Especially in peripheral arterial disease and diabetic foot syndrome, patients showed nearly

the same risk comparing well controlled double diabetes and not well controlled diabetes type 1 without MS (Fig. 2). These data suggest that double diabetes entails a higher risk for any type of macrovascular comorbidities resulting in a higher prevalence of such events compared to data of UKPDS, EDC, EDIC or EURODIAB [28, 31, 32]. Double diabetes subjects thereby show a risk for cardiovascular comorbidities similar to patients with T2DM. Efforts are required to address the clinical problem of obesity and MS in persons with T1DM in order to reduce the risk for late complications. The number of people with T1DM and MS who are treated additionally with insulin resistance lowering substances as Metformin or weight reducing substances as GLP-1 (glucagon like peptide 1)-analogues are still too small to see a possible effect. Here clinical trials should evaluate the output of different methods of weight and insulin resistance reduction in people with T1DM.

Microvascular comorbidities are known to be linked to blood sugar control [33], but patients with T2DM are known to have a higher risk of diabetic nephropathy than people with T1DM [34]. In our study, subjects with double diabetes show a significantly higher prevalence of diabetic nephropathy than T1DM without MS (Fig. 3) [2], which was comparable to that seen in T2DM [33].

Diabetic retinopathy was also more prevalent in persons with double diabetes (Fig. 3) [2]. People with good metabolic control had a lower prevalence of non proliferative retinopathy in both the obese and non-obese groups. Here the risk in developing eye complications was more dependent on blood sugar control than on insulin resistance. However, the presence of MS in the subgroup of persons with well controlled diabetes increased risk significantly.

#### **4.1. Limitations of the study**

A minimal selection bias might not be totally excluded in the group of uncomplicated diabetes type 1, since some of them have been treated only by their family doctor and different centers might use heterogeneous documentations.

The macrovascular events are evaluated retrospectively and not prospectively, which might also cause differences.

HbA1c levels were not measured centrally. In order to reduce inter laboratory variations of HbA1c values, they were standardized according to DCCT, using the multiple of the mean method.

## **4.2. Conclusion**

Taking together, MS in T1DM is associated with increased prevalence of macro- and microvascular complications, even in those with good glycaemic control. Lifestyle modifications as physical exercise, healthy diet and weight reduction have to be acknowledged as essential therapeutic strategies, not only for type 2 but also for T1DM persons, in order to improve quality of life and survival. People with double diabetes are a special risk population, because the awareness for their metabolic comorbidities is lacking and stronger efforts are necessary to identify these patients and explore strategies to reduce the rate of MS in T1DM.

## **Acknowledgments**

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## **Author Contributions**

Conceived and designed the experiments: SRM. Analysed the data: RWH. Contributed analysis tools: RWH. Wrote the paper: SRM. Contributed to the discussion: WK, MS, AZ, MMK, RWH. Reviewed the manuscript: WK, FB, MS, AZ, PJ, MMK, RWH.

**Figures:**

**Figure 1:** Selection of study population from the DPV database, MS was defined according to the NCEP criteria, if participants show at least three criteria out of obesity (waist circumference > 40 inches in male, >35 inches in female or BMI>30kg/m<sup>2</sup>), hyperglycaemia which all participants show since all are diagnosed with diabetes mellitus, dyslipidaemia or arterial hypertension.

**Table 1:** Baseline characteristics of all persons from DPV database, for T1DM people with (double diabetes) or without MS (T1DM w/o MS) as defined by NCEP criteria.

**Table 2:** Baseline clinical characteristics of persons from DPV database, for T1DM people with (double diabetes) or without MS (T1DM w/o MS) as defined by NCEP criteria. Data were adjusted for sex, age and diabetes as mentioned in Material and Methods.

**Figure 2:** prevalence of macrovascular diseases in people with T1DM mellitus, the data present the percentage of persons in relation to all persons with double diabetes (n=7926) or in relation to people with T1DM without MS (T1DM w/o MS, n= 23193). Double diabetes all: all people with type1 diabetes and MS; double diabetes, HbA1c<7% (53mmol/mol): persons with double diabetes with good blood glucose control (n=1892); T1DM w/o MS all: all persons with T1DM who did not meet the NCEP criteria of the MS (n=23193); T1DM w/o MS HbA1c<7% (53mmol/mol): persons with T1DM and good glucose control who did not meet the NCEP criteria of the MS (n=7311). Data were adjusted for sex, age and diabetes as mentioned in Material and Methods

**Figure 3:** prevalence of microvascular diseases in people with T1DM mellitus, the data present the percentage of persons in relation all persons with double diabetes or in relation to people with T1DM without MS (T1DM w/o MS). Double diabetes all: all people with type1 diabetes and MS(n=6502); double diabetes, HbA1c<7% (53mmol/mol): persons with double diabetes with good blood glucose control (n=1512); T1DM w/o MS all: all persons with T1DM who did not meet the NCEP criteria of the MS (n=16721); T1DM w/o MS HbA1c<7% (53mmol/mol): persons with T1DM who did not meet the NCEP criteria of the MS but show HbA1c <7% (53mmol/mol) (n=5072). Data were adjusted for sex, age and diabetes as mentioned in Material and Methods

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**Conflicts of interest** The authors have no conflict of interest to declare.

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**Figure 1:** Selection of study population from the DPV database, MS was defined according to the NCEP criteria, if participants show at least three criteria out of obesity (waist circumference > 40 inches in male, >35 inches in female or BMI>30kg/m<sup>2</sup>), hyperglycaemia which all participants show since all are diagnosed with diabetes mellitus, dyslipidaemia or arterial hypertension.

**Table 1:** Baseline characteristics of all persons from DPV database, for T1DM people with (double diabetes) or without MS (T1DM w/o MS) as defined by NCEP criteria.

**Table 2:** Baseline clinical characteristics of persons from DPV database, for T1DM people with (double diabetes) or without MS (T1DM w/o MS) as defined by NCEP criteria. Data were adjusted for sex, age and diabetes as mentioned in Material and Methods.

**Figure 2:** prevalence of macrovascular diseases in people with T1DM mellitus, the data present the percentage of persons in relation to all persons with double diabetes (n=7926) or in relation to people with T1DM without MS (T1DM w/o MS, n= 23193). Double diabetes all: all people with type1 diabetes and MS; double diabetes, HbA1c<7% (53mmol/mol): persons with double diabetes with good blood glucose control (n=1892); T1DM w/o MS all: all persons with T1DM who did not meet the NCEP criteria of the MS (n=23193); T1DM w/o MS HbA1c<7% (53mmol/mol): persons with T1DM and good glucose control who did not meet the NCEP criteria of the MS (n=7311). Data were adjusted for sex, age and diabetes as mentioned in Material and Methods

**Figure 3:** prevalence of microvascular diseases in people with T1DM mellitus, the data present the percentage of persons in relation all persons with double diabetes or in relation to people with T1DM without MS (T1DM w/o MS). Double diabetes all: all people with type1 diabetes and MS(n=6502); double diabetes, HbA1c<7% (53mmol/mol): persons with double diabetes

with good blood glucose control (n=1512); T1DM w/o MS all: all persons with T1DM who did not meet the NCEP criteria of the MS (n=16721); T1DM w/o MS HbA1c<7% (53mmol/mol): persons with T1DM who did not meet the NCEP criteria of the MS but show HbA1c <7% (53mmol/mol) (n=5072). Data were adjusted for sex, age and diabetes as mentioned in Material and Methods

Table 1:

	double diabetes		T1DM w/o MS		p-value	p-value
	all	HbA1c<7% (53mmol/m ol)	all	HbA1c<7% (53mmol/m ol)	all	HbA1c<7% (53mmol/m ol)
numbers	7926	1892	23193	7311	n.a	n.a
male (%)	54.3	55.7	53.1	54.2	n.a	n.a
female (%)	44.7	44.3	44.8	45.8	n.a	n.a
age (y)	44.7 ± 18.6	50.6 ± 17.8	36.2 ± 18.3	40.2 ± 18.9	<0.0001	<0.0001
diabetes duration (y)	17.6 ± 14.1	21.2 ±14.9	15.0 ± 12.7	17.1 ± 14.0	<0.0001	<0.0001
age at diagnosis (y)	27.1 ± 16.8	29.3 ± 16.8	21.2 ± 15.3	23.1 ± 15.3	<0.0001	<0.0001
<b>insulin regime</b>						
ICT	64.0	62.7	61.9	60.7	0.0013	0.9021
CSII	21.2	20.5	23.6	22.3	<0.0001	0.8023

Table 2:

	double diabetes		T1DM w/o MS		p-value	p-value
	all	HbA1c<7% (53mmol/mol)	all	HbA1c<7% (53mmol/mol)	all	HbA1c<7% (53mmol/mol)
BMI (kg/m <sup>2</sup> )	28.9 ± 7.1	29.7 ± 5.7	24.0 ± 5.1	24.3 ± 6.8	<0.0001	<0.0001
BMI < 19kg/m <sup>2</sup> (%)	2.0	1.4	4.7	3.7	n.a	n.a
BMI 19-24.99kg/m <sup>2</sup> (%)	26.7	20.3	60.1	59.1	n.a	n.a
BMI 25-29.99kg/m <sup>2</sup> (%)	26.9	27.1	32.2	34.2	n.a	n.a
BMI 30-34.99kg/m <sup>2</sup> (%)	31.5	37.1	2.3	2.3	n.a	n.a
BMI>35kg/m <sup>2</sup> (%)	12.9	14.0	0.6	0.7	n.a	n.a
waist (cm)	98.9 ± 32.2	99.3 ± 12.2	84.9 ± 10.3	85.8 ± 10.5	<0.0001	<0.0001
HbA1c (%) (mmol/mol)	8.5 ± 0.051 69 ± 0.7	6.3±0.01 45. ± 0.00	8.0 ± 0.048 64.± 1.0	6.3±0.01 45± 0.00	<0.0001	n.a
insulin dose (I.U.) per day	71.34 ± 0.64	65.97 ± 0.81	56.09 ± 0.59	49.92±0.59	<0.0001	<0.0001
insulin dose (I.U.) per kg BW	0.865±0.0087	0.782±0.010	0.801 ± 0.0080	0.711±0.008	<0.0001	<0.0001
Dyslipidemia (%)	84.1	78.4	53.9	47.9	<0.0001	<0.0001
LDL mg/dl	116.2 ± 45.2	110.3 ± 44.7	103.8 ± 36.6	101.1 ± 35.6	<0.0001	<0.0001
HDL (mg/dl)	49.4 ± 21.1	49.9 ± 9	65.8 ± 20.5	67.7 ± 19.8	<0.0001	<0.0001
triglycerides (mg/dl)	206.1 ± 162.5	177,1 ± 128.3	100.7 ± 68.1	87.9 ± 14.2	<0.0001	<0.0001
arterial Hypertension (%)	40.5	44.1	23.3	24.0	<0.0001	<0.0001
systolic BP (mmHg)	134.4 ± 15.8	135.2 ± 15.8	125.6 ± 15.0	126.1 ± 15.4	<0.0001	<0.0001

diastolic BP (mmHg)	78.4 ± 10.1	77.8 ± 10.3	74.4 ± 9.8	74.3 ± 10.3	<0.0001	<0.0001
smoker (%)	23.0	17.9	21.4	16.0	0.0104	0.1143
diabetes specific antibodies						
GAD (%)	87.8	89.7	84.9	85.2	0.7165	0.9948
IA2 (%)	68.5	71.4	72.0	75.1	0.7100	0.9252
ICA (%)	63.1	66.2	70.2	73.4	0.2511	0.6930
Thyroid antibodies (%)	24.9	26.2	25.6	24.9	0.5461	0.8059
Clinical diagnosis of coeliac disease (%)	0.7	0.4	1.2	1.2	0.1767	0.0470

T1DM >18 y  
n = 40046

Patients with no documented BMI  
or not documented insulin dose  
n = 7175

BMI/insulin dose documented  
n = 32871

Patients without measured  
diabetes specific antibodies  
n = 1498

Patients with additional  
sulfonylurea therapy  
n = 254

People with T1DM with measured  
Diabetes specific antibodies and without  
sulfonylurea comedication  
n = 31119

Patients with at least 3 criteria of  
a metabolic syndrome

Double Diabetes  
n = 7926

Double Diabetes,  
well controlled  
(HbA1c < 7%)  
n = 1892

Patients, who did not fulfill the  
NCEP definition of Metabolic  
syndrome

T1DM w/o MS  
n = 23193

T1DM w/o MS,  
well controlled  
(HbA1c < 7%)  
n = 7311



